

## 6843.0052.00000.txt SEQUENCE LISTING

<110> Khare, Sanjay D.

<120> COMBINATION THERAPY WITH CO-STIMULATORY FACTORS

<130> 06843.0052-00000

<140> US 10/748,112

<141> 2003-12-29

<150> US 60/437,405

<151> 2002-12-30

<160> 28

<170> PatentIn version 3.2

<210> 1

<211> 293

<212> PRT

<213> Artificial Sequence

<220>

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Ser Ser Gly Ser Gly Ser Ala Thr His Met Leu Pro Gly Cys Lys Trp 35 40 45

Asp Leu Leu Ile Lys Gln Trp Val Cys Asp Pro Leu Gly Gly Gly 50 60

Gly Val Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu 65 70 75 80

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr 85 90 95

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Asp Val
100 105 110

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val 115 120 125

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser 130 135 140 Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu 145 150 155 160

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala 165 170 175

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro 180 185 190

Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln 195 200 205

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala 210 215 220

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr 225 230 235 240

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu 245 250 255

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser 260 265 270

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser 275 280 285

Leu Ser Pro Gly Lys 290

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<213> Homo sapiens

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Arg Val Thr Val Leu Arg Gln Ala Asp Ser Gln Val Thr Glu Val Cys 35 40 45

Ala Ala Thr Tyr Met Met Gly Asn Glu Leu Thr Phe Leu Asp Asp Ser 50 60

Ile Cys Thr Gly Thr Ser Ser Gly Asn Gln Val Asn Leu Thr Ile Gln Page 2 Gly Leu Arg Ala Met Asp Thr Gly Leu Tyr Ile Cys Lys Val Glu Leu 85 90 95

Met Tyr Pro Pro Pro Tyr Tyr Leu Gly Ile Gly Asn Gly Thr Gln Ile 100 105 110

Tyr Val Ile Asp Pro Glu Pro Cys Pro Asp Ser Asp Phe Leu Leu Trp 115 120 125

Ile Leu Ala Ala Val Ser Ser Gly Leu Phe Phe Tyr Ser Phe Leu Leu 130 135 140

Thr Ala Val Ser Leu Ser Lys Met Leu Lys Lys Arg Ser Pro Leu Thr 145 150 155 160

Thr Gly Val Tyr Val Lys Met Pro Pro Thr Glu Pro Glu Cys Glu Lys
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Gln Phe Gln Pro Tyr Phe Ile Pro Ile Asn 180 185

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Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly 50 60

Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln 65 70 75 80

Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp 85 90 95

Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe  $100 \hspace{1cm} 105 \hspace{1cm} 110$ Glu Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala 115 120 125 Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr Lys Phe Tyr Phe Gln Glu Asp Glu Ala Ala Ala Glu Pro Lys Ser 150 Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu 165 170 175 Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu 180 185 190 Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Asp Val Ser 195 200 205 His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu 210 215 220 Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr 225 230 235 240 Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn 245 250 255 Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro 260 265 270 Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln 275 280 285 Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val 290 295 300 Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val 305 310 315 Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro 325 330 335 Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr 340 345 350 Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val 355 360 365 Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu 370 380 Ser Pro Gly Lys <210> 106 <211> <212> PRT <213> Artificial Sequence <220> <223> s-TNFR-I amino acid sequence <400> Met Asp Ser Val Cys Pro Gln Gly Lys Tyr Ile His Pro Gln Asn Asn 1 10 15 Ser Ile Cys Cys Thr Lys Cys His Lys Gly Thr Tyr Leu Tyr Asn Asp 20 25 30 Cys Pro Gly Pro Gly Gln Asp Thr Asp Cys Arg Glu Cys Glu Ser Gly 35 40 45 Ser Phe Thr Ala Ser Glu Asn His Leu Arg His Cys Leu Ser Cys Ser 50 60 Lys Cys Arg Lys Glu Met Gly Gln Val Glu Ile Ser Ser Cys Thr Val 65 70 75 80 Asp Arg Asp Thr Val Cys Gly Cys Arg Lys Asn Gln Tyr Arg His Tyr 85 90 95Trp Ser Glu Asn Leu Phe Gln Cys Phe Asn <210> 1167 <212> DNA Artificial Sequence <220> <223> IL-1 inhibitor (KIN2 )(FcIL-1ra) nucleotide sequence <400> atgcgaccgt ccggccgtaa gagctccaaa atgcaggctt tccgtatctg ggacgttaac

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120

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<220>
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acggactgca gggagtgtga gagcggctcc ttcaccgctt cagaaaacca cctcagacac
                                                                     180
tgcctcagct gctccaaatg ccgaaaggaa atgggtcagg tggagatctc ttcttgcaca
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<sup>:213&</sup>gt; Homo sapiens

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85 90 95 Val Val Arg Asn Ser Ser Tyr Cys Leu Arg Ile Lys Ile Ser Ala Lys 100 105 110Phe Val Glu Asn Glu Pro Asn Leu Cys Tyr Asn Ala Gln Ala Ile Phe 115 120 125 Lys Gln Lys Leu Pro Val Ala Gly Asp Gly Gly Leu Val Cys Pro Tyr Met Glu Phe Phe Lys Asn Glu Asn Asn Glu Leu Pro Lys Leu Gln Trp Tyr Lys Asp Cys Lys Pro Leu Leu Leu Asp Asn Ile His Phe Ser Gly 165 170 175 Val Lys Asp Arg Leu Ile Val Met Asn Val Ala Glu Lys His Arg Gly 180 185 190 Asn Tyr Thr Cys His Ala Ser Tyr Thr Tyr Leu Gly Lys Gln Tyr Pro 195 200 205 Ile Thr Arg Val Ile Glu Phe Ile Thr Leu Glu Glu Asn Lys Pro Thr Arg Pro Val Ile Val Ser Pro Ala Asn Glu Thr Met Glu Val Asp Leu 225 230 Gly Ser Gln Ile Gln Leu Ile Cys Asn Val Thr Gly Gln Leu Ser Asp 250 Page 7

Ile Ala Tyr Trp Lys Trp Asn Gly Ser Val Ile Asp Glu Asp Asp Pro 260 265 270 Val Leu Gly Glu Asp Tyr Tyr Ser Val Glu Asn Pro Ala Asn Lys Arg 275 280 285 Arg Ser Thr Leu Ile Thr Val Leu Asn Ile Ser Glu Ile Glu Ser Arg 290 295 300 Phe Tyr Lys His Pro Phe Thr Cys Phe Ala Lys Asn Thr His Gly Ile 305 310 315 320 Asp Ala Ala Tyr Ile Gln Leu Ile Tyr Pro Val Thr Asn Phe Gln Lys 325 330 335 His Met Ile Gly Ile Cys Val Thr Leu Thr Val Ile Ile Val Cys Ser 340 350 Val Phe Ile Tyr Lys Ile Phe Lys Ile Asp Ile Val Leu Trp Tyr Arg 355 360 365 Asp Ser Cys Tyr Asp Phe Leu Pro Ile Lys Ala Ser Asp Gly Lys Thr 370 375 380 Tyr Asp Ala Tyr Ile Leu Tyr Pro Lys Thr Val Gly Glu Gly Ser Thr 385 390 395 400 Ser Asp Cys Asp Ile Phe Val Phe Lys Val Leu Pro Glu Val Leu Glu 405 410 415 Lys Gln Cys Gly Tyr Lys Leu Phe Ile Tyr Gly Arg Asp Asp Tyr Val 420 425 430 Gly Glu Asp Ile Val Glu Val Ile Asn Glu Asn Val Lys Lys Ser Arg 435 440 445 Arg Leu Ile Ile Leu Val Arg Glu Thr Ser Gly Phe Ser Trp Leu 450 460 Gly Gly Ser Ser Glu Glu Gln Ile Ala Met Tyr Asn Ala Leu Val Gln 465 470 475 480 Asp Gly Ile Lys Val Val Leu Leu Glu Leu Glu Lys Ile Gln Asp Tyr 485 490 495 Glu Lys Met Pro Glu Ser Ile Lys Phe Ile Lys Gln Lys His Gly Ala 505 Page 8

Ile Arg Trp Ser Gly Asp Phe Thr Gln Gly Pro Gln Ser Ala Lys Thr 515 520 525

Arg Phe Trp Lys Asn Val Arg Tyr His Met Pro Val Gln Arg Arg Ser 530 540

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<211> 455

<212> PRT

<213> Homo sapiens

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His Leu Gly Asp Arg Glu Lys Arg Asp Ser Val Cys Pro Gln Gly Lys 35 40 45

Tyr Ile His Pro Gln Asn Asn Ser Ile Cys Cys Thr Lys Cys His Lys 50 60

Gly Thr Tyr Leu Tyr Asn Asp Cys Pro Gly Pro Gly Gln Asp Thr Asp 65 70 75 80

Cys Arg Glu Cys Glu Ser Gly Ser Phe Thr Ala Ser Glu Asn His Leu 85 90 95

Arg His Cys Leu Ser Cys Ser Lys Cys Arg Lys Glu Met Gly Gln Val 100 105 110

Glu Ile Ser Ser Cys Thr Val Asp Arg Asp Thr Val Cys Gly Cys Arg 115 120 125

Lys Asn Gln Tyr Arg His Tyr Trp Ser Glu Asn Leu Phe Gln Cys Phe 130 140

Asn Cys Ser Leu Cys Leu Asn Gly Thr Val His Leu Ser Cys Gln Glu 145 150 155 160 Lys Gln Asn Thr Val Cys Thr Cys His Ala Gly Phe Phe Leu Arg Glu 165 170 175 Asn Glu Cys Val Ser Cys Ser Asn Cys Lys Lys Ser Leu Glu Cys Thr 180 185 190 Lys Leu Cys Leu Pro Gln Ile Glu Asn Val Lys Gly Thr Glu Asp Ser Gly Thr Thr Val Leu Leu Pro Leu Val Ile Phe Phe Gly Leu Cys Leu Leu Ser Leu Leu Phe Ile Gly Leu Met Tyr Arg Tyr Gln Arg Trp Lys 225 230 235 240 Ser Lys Leu Tyr Ser Ile Val Cys Gly Lys Ser Thr Pro Glu Lys Glu 245 250 255 Gly Glu Leu Glu Gly Thr Thr Thr Lys Pro Leu Ala Pro Asn Pro Ser 260 265 270 Phe Ser Pro Thr Pro Gly Phe Thr Pro Thr Leu Gly Phe Ser Pro Val Pro Ser Ser Thr Phe Thr Ser Ser Ser Thr Tyr Thr Pro Gly Asp Cys 290 295 300 Pro Asn Phe Ala Ala Pro Arg Arg Glu Val Ala Pro Pro Tyr Gln Gly 305 310 315 Ala Asp Pro Ile Leu Ala Thr Ala Leu Ala Ser Asp Pro Ile Pro Asn 325 330 335 Pro Leu Gln Lys Trp Glu Asp Ser Ala His Lys Pro Gln Ser Leu Asp 340 345 350 Thr Asp Asp Pro Ala Thr Leu Tyr Ala Val Val Glu Asn Val Pro Pro 355 360 365 Leu Arg Trp Lys Glu Phe Val Arg Arg Leu Gly Leu Ser Asp His Glu 370 380 Ile Asp Arg Leu Glu Leu Gln Asn Gly Arg Cys Leu Arg Glu Ala Gln 385 390 395 400 Tyr Ser Met Leu Ala Thr Trp Arg Arg Thr Pro Arg Arg Glu Ala 41Ŏ Page 10

Thr Leu Glu Leu Leu Gly Arg Val Leu Arg Asp Met Asp Leu Leu Gly 420 425 430

Cys Leu Glu Asp Ile Glu Glu Ala Leu Cys Gly Pro Ala Ala Leu Pro 435 440 445

Pro Ala Pro Ser Leu Leu Arg 450 455

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<211> 461

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<213> Homo sapiens

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Ala Pro Glu Pro Gly Ser Thr Cys Arg Leu Arg Glu Tyr Tyr Asp Gln 35 40 45

Thr Ala Gln Met Cys Cys Ser Lys Cys Ser Pro Gly Gln His Ala Lys 50 60

Val Phe Cys Thr Lys Thr Ser Asp Thr Val Cys Asp Ser Cys Glu Asp 65 70 75 80

Ser Thr Tyr Thr Gln Leu Trp Asn Trp Val Pro Glu Cys Leu Ser Cys 85 90 95

Gly Ser Arg Cys Ser Ser Asp Gln Val Glu Thr Gln Ala Cys Thr Arg 100 105 110

Glu Gln Asn Arg Ile Cys Thr Cys Arg Pro Gly Trp Tyr Cys Ala Leu 115 120 125

Ser Lys Gln Glu Gly Cys Arg Leu Cys Ala Pro Leu Arg Lys Cys Arg 130 135 140

Pro Gly Phe Gly Val Ala Arg Pro Gly Thr Glu Thr Ser Asp Val Val 145 150 155 160

Cys Lys Pro Cys Ala Pro Gly Thr Phe Ser Asn Thr Thr Ser Ser Thr 165 170 175 Asp Ile Cys Arg Pro His Gln Ile Cys Asn Val Val Ala Ile Pro Gly 180 185 190 Asn Ala Ser Met Asp Ala Val Cys Thr Ser Thr Ser Pro Thr Arg Ser 195 200 205 Met Ala Pro Gly Ala Val His Leu Pro Gln Pro Val Ser Thr Arg Ser Gln His Thr Gln Pro Thr Pro Glu Pro Ser Thr Ala Pro Ser Thr Ser Phe Leu Leu Pro Met Gly Pro Ser Pro Pro Ala Glu Gly Ser Thr Gly Asp Phe Ala Leu Pro Val Gly Leu Ile Val Gly Val Thr Ala Leu Gly 260 265 270 Leu Leu Ile Gly Val Val Asn Cys Val Ile Met Thr Gln Val Lys Lys Lys Pro Leu Cys Leu Gln Arg Glu Ala Lys Val Pro His Leu Pro 290 295 300 Ala Asp Lys Ala Arg Gly Thr Gln Gly Pro Glu Gln Gln His Leu Leu 305 310 315 320 Ile Thr Ala Pro Ser Ser Ser Ser Ser Leu Glu Ser Ser Ala Ser 325 330 335 Ala Leu Asp Arg Arg Ala Pro Thr Arg Asn Gln Pro Gln Ala Pro Gly 340 345 350 val Glu Ala Ser Gly Ala Gly Glu Ala Arg Ala Ser Thr Gly Ser Ser Asp Ser Ser Pro Gly Gly His Gly Thr Gln Val Asn Val Thr Cys Ile 370 380 Val Asn Val Cys Ser Ser Ser Asp His Ser Ser Gln Cys Ser Ser Gln Ala Ser Ser Thr Met Gly Asp Thr Asp Ser Ser Pro Ser Glu Ser Pro Lys Asp Glu Gln Val Pro Phe Ser Lys Glu Glu Cys Ala Phe Arg Ser 420 425 430

Gln Leu Glu Thr Pro Glu Thr Leu Leu Gly Ser Thr Glu Glu Lys Pro 435 440 445

Leu Pro Leu Gly Val Pro Asp Ala Gly Met Lys Pro Ser 450 455 460

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<211> 277 <212> PRT

<213> Homo sapiens

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Ala Val His Pro Glu Pro Pro Thr Ala Cys Arg Glu Lys Gln Tyr Leu 20 25 30

Ile Asn Ser Gln Cys Cys Ser Leu Cys Gln Pro Gly Gln Lys Leu Val 35 40 45

Ser Asp Cys Thr Glu Phe Thr Glu Thr Glu Cys Leu Pro Cys Gly Glu 50 60

Ser Glu Phe Leu Asp Thr Trp Asn Arg Glu Thr His Cys His Gln His 65 70 75 80

Lys Tyr Cys Asp Pro Asn Leu Gly Leu Arg Val Gln Gln Lys Gly Thr 85 90 95

Ser Glu Thr Asp Thr Ile Cys Thr Cys Glu Glu Gly Trp His Cys Thr 100 105 110

Ser Glu Ala Cys Glu Ser Cys Val Leu His Arg Ser Cys Ser Pro Gly 115 120 125

Phe Gly Val Lys Gln Ile Ala Thr Gly Val Ser Asp Thr Ile Cys Glu 130 135 140

Pro Cys Pro Val Gly Phe Phe Ser Asn Val Ser Ser Ala Phe Glu Lys 145 150 155 160

Cys His Pro Trp Thr Ser Cys Glu Thr Lys Asp Leu Val Val Gln Gln 175

Ala Gly Thr Asn Lys Thr Asp Val Val Cys Gly Pro Gln Asp Arg Leu 180 185 190

Arg Ala Leu Val Val Ile Pro Ile Ile Phe Gly Ile Leu Phe Ala Ile Page 13 195 200 205

Leu Leu Val Leu Val Phe Ile Lys Lys Val Ala Lys Lys Pro Thr Asn 210 215 220

Lys Ala Pro His Pro Lys Gln Glu Pro Gln Glu Ile Asn Phe Pro Asp 225 230 235 240

Asp Leu Pro Gly Ser Asn Thr Ala Ala Pro Val Gln Glu Thr Leu His 245 250 255

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Val Gln Glu Arg Gln 275

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<211> 595

<212> PRT

<213> Homo sapiens

<400> 11

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Pro Ser His Tyr Tyr Asp Lys Ala Val Arg Arg Cys Cys Tyr Arg Cys 35 40 45

Pro Met Gly Leu Phe Pro Thr Gln Gln Cys Pro Gln Arg Pro Thr Asp 50 55 60

Cys Arg Lys Gln Cys Glu Pro Asp Tyr Tyr Leu Asp Glu Ala Asp Arg 65 70 75 80

Cys Thr Ala Cys Val Thr Cys Ser Arg Asp Asp Leu Val Glu Lys Thr 85 90 95

Pro Cys Ala Trp Asn Ser Ser Arg Val Cys Glu Cys Arg Pro Gly Met 100 105 110

Phe Cys Ser Thr Ser Ala Val Asn Ser Cys Ala Arg Cys Phe Phe His 115 120 125

Ser Val Cys Pro Ala Gly Met Ile Val Lys Phe Pro Gly Thr Ala Gln 130 135 140 Page 14

Lys Asn Thr Val Cys Glu Pro Ala Ser Pro Gly Val Ser Pro Ala Cys 145 150 155 160 Ala Ser Pro Glu Asn Cys Lys Glu Pro Ser Ser Gly Thr Ile Pro Gln 165 170 175 Ala Lys Pro Thr Pro Val Ser Pro Ala Thr Ser Ser Ala Ser Thr Met 180 185 190 Pro Val Arg Gly Gly Thr Arg Leu Ala Gln Glu Ala Ala Ser Lys Leu 195 200 205 Thr Arg Ala Pro Asp Ser Pro Ser Ser Val Gly Arg Pro Ser Ser Asp 210 215 220 Pro Gly Leu Ser Pro Thr Gln Pro Cys Pro Glu Gly Ser Gly Asp Cys 225 230 235 240 Arg Lys Gln Cys Glu Pro Asp Tyr Tyr Leu Asp Glu Ala Gly Arg Cys 245 250 255 Thr Ala Cys Val Ser Cys Ser Arg Asp Asp Leu Val Glu Lys Thr Pro 260 265 270 Cys Ala Trp Asn Ser Ser Arg Thr Cys Glu Cys Arg Pro Gly Met Ile 275 280 285 Cys Ala Thr Ser Ala Thr Asn Ser Cys Ala Arg Cys Val Pro Tyr Pro 290 295 300 Ile Cys Ala Ala Glu Thr Val Thr Lys Pro Gln Asp Met Ala Glu Lys 305 310 315 Asp Thr Thr Phe Glu Ala Pro Pro Leu Gly Thr Gln Pro Asp Cys Asn 325 330 335 Pro Thr Pro Glu Asn Gly Glu Ala Pro Ala Ser Thr Ser Pro Thr Gln 340 350 Ser Leu Leu Val Asp Ser Gln Ala Ser Lys Thr Leu Pro Ile Pro Thr Ser Ala Pro Val Ala Leu Ser Ser Thr Gly Lys Pro Val Leu Asp Ala 370 375 380 Gly Pro Val Leu Phe Trp Val Ile Leu Val Leu Val Val Val Gly 385 390 395 400 Page 15

Ser Ser Ala Phe Leu Cys His Arg Arg Ala Cys Arg Lys Arg Ile 405 410 415

Arg Gln Lys Leu His Leu Cys Tyr Pro Val Gln Thr Ser Gln Pro Lys 420 425 430

Leu Glu Leu Val Asp Ser Arg Pro Arg Arg Ser Ser Thr Gln Leu Arg 435 440 445

Ser Gly Ala Ser Val Thr Glu Pro Val Ala Glu Glu Arg Gly Leu Met 450 455 460

Ser Gln Pro Leu Met Glu Thr Cys His Ser Val Gly Ala Ala Tyr Leu 465 470 475 480

Glu Ser Leu Pro Leu Gln Asp Ala Ser Pro Ala Gly Gly Pro Ser Ser 485 490 495

Pro Arg Asp Leu Pro Glu Pro Arg Val Ser Thr Glu His Thr Asn Asn 500 505 510

Lys Ile Glu Lys Ile Tyr Ile Met Lys Ala Asp Thr Val Ile Val Gly
515 520 525

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Glu Pro Glu Leu Glu Glu Leu Glu Ala Asp His Thr Pro His Tyr 545 550 555 560

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Leu Ser Val Glu Glu Glu Gly Lys Glu Asp Pro Leu Pro Thr Ala Ala . 580 585 590

Ser Gly Lys 595

<210> 12

<211> 199

<212> PRT <213> Homo sapiens

<400> 12

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<211> 220 <212> PRT

<213> Homo sapiens

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Arg Glu Phe Arg Ala Ser Leu His Lys Gly Leu Asp Ser Ala Val Glu 50 60

Val Cys Val Val Tyr Gly Asn Tyr Ser Gln Gln Leu Gln Val Tyr Ser 65 70 75 80

Lys Thr Gly Phe Asn Cys Asp Gly Lys Leu Gly Asn Glu Ser Val Thr 85 90 95

Phe Tyr Leu Gln Asn Leu Tyr Val Asn Gln Thr Asp Ile Tyr Phe Cys 100 105 110

Lys Ile Glu Val Met Tyr Pro Pro Pro Tyr Leu Asp Asn Glu Lys Ser 115 120 125

Asn Gly Thr Ile Ile His Val Lys Gly Lys His Leu Cys Pro Ser Pro 130 135 140

Leu Phe Pro Gly Pro Ser Lys Pro Phe Trp Val Leu Val Val Gly 145 150 155 160

Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile Ile 165 170 175

Phe Trp Val Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met 180 185 190

Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro 195 200 205

Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser 210 215 220

<210> 14 <211> 277

<211> 277<212> PRT

<213> Homo sapiens

<400> 14

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Gly Asp Thr Tyr Pro Ser Asn Asp Arg Cys Cys His Glu Cys Arg Pro Page 18

45

40

Gly Asn Gly Met Val Ser Arg Cys Ser Arg Ser Gln Asn Thr Val Cys 50 60 Arg Pro Cys Gly Pro Gly Phe Tyr Asn Asp Val Val Ser Ser Lys Pro 65 70 75 80 Cys Lys Pro Cys Thr Trp Cys Asn Leu Arg Ser Gly Ser Glu Arg Lys 85 90 95 Gln Leu Cys Thr Ala Thr Gln Asp Thr Val Cys Arg Cys Arg Ala Gly 100 105 110 Thr Gln Pro Leu Asp Ser Tyr Lys Pro Gly Val Asp Cys Ala Pro Cys 115 120 125 Pro Pro Gly His Phe Ser Pro Gly Asp Asn Gln Ala Cys Lys Pro Trp 130 135 140 Thr Asn Cys Thr Leu Ala Gly Lys His Thr Leu Gln Pro Ala Ser Asn 145 150 155 160 Ser Ser Asp Ala Ile Cys Glu Asp Arg Asp Pro Pro Ala Thr Gln Pro 165 170 175 Gln Glu Thr Gln Gly Pro Pro Ala Arg Pro Ile Thr Val Gln Pro Thr 180 185 190 Glu Ala Trp Pro Arg Thr Ser Gln Gly Pro Ser Thr Arg Pro Val Glu 195 200 205 Pro Gly Gly Arg Ala Val Ala Ala Ile Leu Gly Leu Gly Leu Val 210 220 Leu Gly Leu Leu Gly Pro Leu Ala Ile Leu Leu Ala Leu Tyr Leu Leu 225 230 235 240 Arg Arg Asp Gln Arg Leu Pro Pro Asp Ala His Lys Pro Pro Gly Gly 245 250 255 Gly Ser Phe Arg Thr Pro Ile Gln Glu Glu Gln Ala Asp Ala His Ser 260 265 270 Thr Leu Ala Lys Ile 275

<210> 15

<211> 255

<212> PRT

<213> Homo sapiens

<400> 15

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Ala Gly Thr Phe Cys Asp Asn Asn Arg Asn Gln Ile Cys Ser Pro Cys 35 40 45

Pro Pro Asn Ser Phe Ser Ser Ala Gly Gly Gln Arg Thr Cys Asp Ile 50 60

Cys Arg Gln Cys Lys Gly Val Phe Arg Thr Arg Lys Glu Cys Ser Ser 65 70 75 80

Thr Ser Asn Ala Glu Cys Asp Cys Thr Pro Gly Phe His Cys Leu Gly 85 90 95

Ala Gly Cys Ser Met Cys Glu Gln Asp Cys Lys Gln Gly Gln Glu Leu 100 105 110

Thr Lys Lys Gly Cys Lys Asp Cys Cys Phe Gly Thr Phe Asn Asp Gln 115 120 125

Lys Arg Gly Ile Cys Arg Pro Trp Thr Asn Cys Ser Leu Asp Gly Lys 130 135 140

Ser Val Leu Val Asn Gly Thr Lys Glu Arg Asp Val Val Cys Gly Pro 145 150 155 160

Ser Pro Ala Asp Leu Ser Pro Gly Ala Ser Ser Val Thr Pro Pro Ala 165 170 175

Pro Ala Arg Glu Pro Gly His Ser Pro Gln Ile Ile Ser Phe Phe Leu 180 185 190

Ala Leu Thr Ser Thr Ala Leu Leu Phe Leu Leu Phe Phe Leu Thr Leu 195 200 205

Arg Phe Ser Val Val Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe 210 220

Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly 225 230 235 240 Page 20

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Tyr Gln Thr Leu Val Asn Ser Thr Ser Leu Tyr Lys Asn Cys Lys Lys 145 . 150 . 155 . 160

Leu Leu Leu Glu Asn Asn Lys Asn Pro Thr Ile Lys Lys Asn Ala Glu Phe Glu Asp Gln Gly Tyr Tyr Ser Cys Val His Phe Leu His His Asn 180 185 190 Gly Lys Leu Phe Asn Ile Thr Lys Thr Phe Asn Ile Thr Ile Val Glu 195 200 205 Asp Arg Ser Asn Ile Val Pro Val Leu Leu Gly Pro Lys Leu Asn His 210 220 Val Ala Val Glu Leu Gly Lys Asn Val Arg Leu Asn Cys Ser Ala Leu 225 230 235 240 Leu Asn Glu Glu Asp Val Ile Tyr Trp Met Phe Gly Glu Glu Asn Gly 245 250 255 Ser Asp Pro Asn Ile His Glu Glu Lys Glu Met Arg Ile Met Thr Pro 260 265 270 Glu Gly Lys Trp His Ala Ser Lys Val Leu Arg Ile Glu Asn Ile Gly 275 280 285 Glu Ser Asn Leu Asn Val Leu Tyr Asn Cys Thr Val Ala Ser Thr Gly 290 295 300 Gly Thr Asp Thr Lys Ser Phe Ile Leu Val Arg Lys Ala Asp Met Ala 305 310 315 Asp Ile Pro Gly His Val Phe Thr Arg Gly Met Ile Ile Ala Val Leu 325 330 335 Ile Leu Val Ala Val Val Cys Leu Val Thr Val Cys Val Ile Tyr Arg 340 345 350 Val Asp Leu Val Leu Phe Tyr Arg His Leu Thr Arg Arg Asp Glu Thr 355 360 365 Leu Thr Asp Gly Lys Thr Tyr Asp Ala Phe Val Ser Tyr Leu Lys Glu 370 380 Cys Arg Pro Glu Asn Gly Glu Glu His Thr Phe Ala Val Glu Ile Leu 385 390 395 400 Pro Arg Val Leu Glu Lys His Phe Gly Tyr Lys Leu Cys Ile Phe Glu 405 410 415 Arg Asp Val Val Pro Gly Gly Ala Val Val Asp Glu Ile His Ser Leu 420 425 430

Ile Glu Lys Ser Arg Arg Leu Ile Ile Val Leu Ser Lys Ser Tyr Met 435 440 445

Ser Asn Glu Val Arg Tyr Glu Leu Glu Ser Gly Leu His Glu Ala Leu 450 455 460

Val Glu Arg Lys Ile Lys Ile Ile Leu Ile Glu Phe Thr Pro Val Thr 465 470 475 480

Asp Phe Thr Phe Leu Pro Gln Ser Leu Lys Leu Leu Lys Ser His Arg 485 490 495

Val Leu Lys Trp Lys Ala Asp Lys Ser Leu Ser Tyr Asn Ser Arg Phe 500 505 510

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Asn Pro Pro Thr Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp 35 40 45

Asn Ala Thr Phe Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val 50 55 60

Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala 65 70 75 80

Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg 85 90 95

Val Thr Gln Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg Page 24

<sup>&</sup>lt;210> 18

<sup>&</sup>lt;211> 288

<sup>&</sup>lt;212> PRT

<sup>&</sup>lt;213> Homo sapiens

Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu 115 120 125 Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val 130 140 Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro 145 150 . 155 160 Arg Ser Ala Gly Gln Phe Gln Thr Leu Val Val Gly Val Val Gly Gly 165 170 175 Leu Leu Gly Ser Leu Val Leu Leu Val Trp Val Leu Ala Val Ile Cys Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala-Arg Arg Thr Gly Gln Pro Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly 210 220 Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro 225 230 235 240 Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly 245 250 255 Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg 260 265 270 Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu 275 280 285

Met Ala Cys Leu Gly Leu Arg Arg Tyr Lys Ala Gln Leu Gln Leu Pro 1 10 15

Ser Arg Thr Trp Pro Phe Val Ala Leu Leu Thr Leu Leu Phe Ile Pro 20 25 30

Val Phe Ser Glu Ala Ile Gln Val Thr Gln Pro Ser Val Val Leu Ala 35 40 45 Page 25

<sup>&</sup>lt;210> <211> 223

<sup>&</sup>lt;212> PRT

Mus musculus

<sup>&</sup>lt;400>

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Homo sapiens <213>

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Glu Ile Ser Pro Cys Lys Ala Asp Met Asp Thr Val Cys Gly Cys Lys 115 120 125 Lys Asn Gln Phe Gln Arg Tyr Leu Ser Glu Thr His Phe Gln Cys Val 130 135 140 Asp Cys Ser Pro Cys Phe Asn Gly Thr Val Thr Ile Pro Cys Lys Glu 145 150 155 160 Lys Gln Asn Thr Val Cys Asn Cys His Ala Gly Phe Phe Leu Ser Gly 165 170 175 Asn Glu Cys Thr Pro Cys Ser His Cys Lys Lys Asn Gln Glu Cys Met 180 185 190 Lys Leu Cys Leu Pro Pro Val Ala Asn Val Thr Asn Pro Gln Asp Ser 195 200 205 Gly Thr Ala Val Leu Leu Pro Leu Val Ile Phe Leu Gly Leu Cys Leu 210 220 Leu Phe Phe Ile Cys Ile Ser Leu Leu Cys Arg Tyr Pro Gln Trp Arg 225 230 235 240 Pro Arg Val Tyr Ser Ile Ile Cys Arg Asp Ser Ala Pro Val Lys Glu 245 250 255 Val Glu Gly Glu Gly Ile Val Thr Lys Pro Leu Thr Pro Ala Ser Ile 260 265 270 Pro Ala Phe Ser Pro Asn Pro Gly Phe Asn Pro Thr Leu Gly Phe Ser 275 280 285 Thr Thr Pro Arg Phe Ser His Pro Val Ser Ser Thr Pro Ile Ser Pro 290 295 300 Val Phe Gly Pro Ser Asn Trp His Asn Phe Val Pro Pro Val Arg Glu 305 310 315 320 Val Val Pro Thr Gln Gly Ala Asp Pro Leu Leu Tyr Gly Ser Leu Asn Pro Val Pro Ile Pro Ala Pro Val Arg Lys Trp Glu Asp Val Val Ala 340 345 350 Ala Gln Pro Gln Arg Leu Asp Thr Ala Asp Pro Ala Met Leu Tyr Ala

Val Val Asp Gly Val Pro Pro Thr Arg Trp Lys Glu Phe Met Arg Leu 370 380

Leu Gly Leu Ser Glu His Glu Ile Glu Arg Leu Glu Leu Gln Asn Gly 385 390 395 400

Arg Cys Leu Arg Glu Ala His Tyr Ser Met Leu Glu Ala Trp Arg Arg 405 410 415

Arg Thr Pro Arg His Glu Ala Thr Leu Asp Val Val Gly Arg Val Leu 420 425 430

Cys Asp Met Asn Leu Arg Gly Cys Leu Glu Asn Ile Arg Glu Thr Leu 435 440 445

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Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr 35 40 45

Cys Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn 50 60

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg 65 70 75 80

Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val 85 90 95

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser 100 105 110

Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys 115 120 125 Page 29

Gly	Gln 130	Pro	Arg	Glu	Pro	Gln 135	val	Tyr	Thr	Leu	Pro 140	Pro	Ser	Arg	Asp		
Glu 145	Leu	Thr	Lys	Asn	Gln 150	val	Ser	Leu	Thr	Cys 155	Leu	val	Lys	Gly	Phe 160		
Tyr	Pro	Ser	Asp	11e 165	Ala	∨al	Glu	Trp	Glu 170	Ser	Asn	Gly	Gln	Pro 175	Glu		
Asn	Asn	Tyr	Lys 180	Thr	Thr	Pro	Pro	val 185	Leu	Asp	Ser	Asp	Gly 190	Ser	Phe		
Phe	Leu	Tyr 195	Ser	Lys	Leu	Thr	va1 200	Asp	Lys	Ser	Arg	Trp 205	Gln	Gln	Gly		
Asn	∨a1 210	Phe	Ser	Cys	Ser	Val 215	Met	His	Glu	Ala	Leu 220	His	Asn	His	Tyr		
Thr 225	Gln	Lys	Ser	Leu	Ser 230	Leu	Ser	Pro	Gly	Lys 235							
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20 25 30
Ser Cys Pro Glu Glu Gln Tyr Trp Asp Pro Leu Leu Gly Thr Cys Met 35 40 45
Ser Cys Lys Thr Ile Cys Asn His Gln Ser Gln Arg Thr Cys Ala Ala 50 60
Phe Cys Arg Ser Leu Ser Cys Arg Lys Glu Gln Gly Lys Phe Tyr Asp 65 70 75 80
His Leu Leu Arg Asp Cys Ile Ser Cys Ala Ser Ile Cys Gly Gln His 85 \hspace{1cm} 90 \hspace{1cm} 95
Pro Lys Gln Cys Ala Tyr Phe Cys Glu Asn Lys Leu Arg Ser Pro Val
100 105 110
Asn Leu Pro Pro Glu Leu Arg Arg Gln Arg Ser Gly Glu Val Glu Asn
115 120 125
Asn Ser Asp Asn Ser Gly Arg Tyr Gln Gly Leu Glu His Arg Gly Ser
130 135 140
Glu Ala Ser Pro Ala Leu Pro Gly Leu Lys Leu Ser Ala Asp Gln Val
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19

Page 31

Ala Leu Val Tyr Ser Thr Leu Gly Leu Cys Leu Cys Ala Val Leu Cys 165 170 175 Cys Phe Leu Val Ala Val Ala Cys Phe Leu Lys Lys Arg Gly Asp Pro 180 185 190

Cys Ser Cys Gln Pro Arg Ser Arg Pro Arg Gln Ser Pro Ala Lys Ser 195 200 205

Ser Gln Asp His Ala Met Glu Ala Gly Ser Pro Val Ser Thr Ser Pro 210 215 220

Glu Pro Val Glu Thr Cys Ser Phe Cys Phe Pro Glu Cys Arg Ala Pro 225 230 235 240

Thr Gln Glu Ser Ala Val Thr Pro Gly Thr Pro Asp Pro Thr Cys Ala 245 250 255

Gly Arg Trp Gly Cys His Thr Arg Thr Thr Val Leu Gln Pro Cys Pro 260 265 270

His Ile Pro Asp Ser Gly Leu Gly Ile Val Cys Val Pro Ala Gln Glu 275 280 285

Gly Gly Pro Gly Ala 290

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